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EXAMINER	
SMITH, CAROLYN L	

ART UNIT	PAPER NUMBER
1631	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/885,827	SALVATI ET AL.	
	Examiner	Art Unit	
	Carolyn L Smith	1631	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the corresp ndence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendments and remarks in Paper No. 17, filed 6/16/03, are acknowledged. Amended claims 1 and 9 and canceled claims 8 and 10-24 are acknowledged.

Applicant's arguments, filed 6/16/03, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from the previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The Information Disclosure Statements, filed 10/15/01, 8/23/02, and 10/11/02, that were not previously considered are addressed below. In the IDS, filed 10/15/01, references AA and AB are now being considered. These are being cited in the 892 form. 10/322,306 and 10/322,077 have also been considered. The abstracts of BM, BN, BP, CF, CG, CH, CI, FS, FU, and FW are being considered. These are being cited in the 892 form. Unfortunately, the copies of CV, CW, CX, FT, and FX (from the 17 page IDS) have been lost and therefore the date of these references is unknown to the Examiner such that they may not be considered at this time. References JA and JB (from the 17 page IDS) have been considered. These are being cited on the 892 form. The search reports KA, KB, KO, KP, KR, and KS are not being acknowledged on the IDS as they do not have a proper publication date. However, these search reports were looked at by the Examiner due to mention of these references being found elsewhere in the disclosure. The Examiner made an inadvertent error by initializing the other search reports (JS-JZ and KC-KT) which are not considered to be printed publications with proper publication dates. These are not being considered officially on the IDS (a copy of pages 15-17 of the

previous IDS is being sent back to Applicants with the Search Reports lined through); however, the Examiner has looked at the references due to their presence being found elsewhere in the disclosure.

Claims 1 (amended), 2-7, and 9 (amended) are herein under examination.

Claims Rejected Under 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

LACK OF SCOPE OF ENABLEMENT

The rejection of claims 1-7 and 9 is maintained under 35 U.S.C. 112, first paragraph.

This rejection is maintained and reiterated below for reasons of record.

Claims 1-7 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the atomic structural coordinate listing (Table A) of an androgen receptor-ligand binding domain (AR-LBD), does not reasonably provide enablement for a method of inhibiting the growth of hormone-dependent tumor cells by administering a selective androgen receptor modulator that exhibits antagonist activity in a hormone-dependent tumor while exhibiting no activity or agonist activity against other non-tumor tissues containing the androgen receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicants state that one "drug design technique enabled in this invention is iterative drug design" (page 10, lines 34-35). Applicants further state that "[i]n iterative drug design, crystals of a series of protein/ligand complexes are obtained" followed by the determination of three-dimensional structures of each complex (page 11, lines 16-19). However, a method that relies on data from an unpredictable art such as protein crystallization would require clear and precise guidance for one skilled in the art to reliably use the said methods. As the science of protein crystallization is well known to be a trial and error procedure with unpredictable results (Drenth, page 1, lines 13-20), one skilled in the art would require clear and precise guidance to make any particular crystal in order to obtain structural coordinates for a three-dimensional model. Accordingly, it would be very difficult for a skilled artisan to make crystal structures of other androgen receptor complexes beyond that mentioned in the instant case where specific coordinates are disclosed. Due to the unpredictability and difficulty of crystallizing proteins, it is unlikely that one of skill in the art would be able to make another crystal relying solely on the information for the crystal disclosed in the specification without undue experimentation. Again, due to the unpredictability in the art, a skilled artisan could not reasonably expect to make and use the structural coordinates from any androgen receptor complex based on generic guidelines of making crystals without undue experimentation.

Applicants' claims are not limited as to the usage of any particular compound type, but rather only limited by assays for growth inhibition. Applicants persuasively argue that assay methodology, such as using cell lines, have been enabled. However, the setting forth of assays alone leaves open a large unpredictable issue as to what compounds to test via the assays to find effective compounds. This is generally unpredictable due to the enormous number of known

compounds. Applicants point to compound types described starting on page 21, line 5, of the specification with compounds shown in Table 1 with the general formulae given as Ia or Ib (page 22 and 26, respectively). Provisional patent applications to support these Ia and Ib compounds are cited on page 22, first full paragraph, as 60/214,392; 60/284617; 60/233519; and 60/284730. Page 3, last paragraph, of each of these provisional applications states that identification of a core structure of non-natural ligands can be achieved by using available crystal structures of a variety of NHR ligand binding domains. It appears that Applicants have only provided an identification of these compounds with the general formulae described above via 3-D modeling of the receptor binding site which does not provide enablement for any compound via merely the knowledge of assays to use to find them.

Claim 9 is further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SARM compounds that were tested in vitro and in vivo to determine whether treatment was effective in remedying a condition in prostate tumors and various cells lines as seen in Examples 2-13 (pages 86-98), does not reasonably provide enablement for a method of treatment of all of the conditions listed in claim 9 by administering an selective androgen receptor modulator (SARM) in an effective amount. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with this claim.

Without further data or sound scientific reasoning, it appears speculative whether these SARMs listed in the specification treat all of the conditions listed in claim 9. As pointed out by Garrard et al., finding effective drugs is not only difficult, but also unpredictable (col. 1, lines 57-67). With this in mind, additional evidence is necessary in order to satisfy the current lack of

scope of enablement for the conditions listed in claim 9. Several options exist to overcome this lack of scope of enablement issue, such as supplying additional data supporting the effective treatment conclusions listed in claim 9 or other scientific reasoning that would lead one of ordinary skill in the art to be able to make and/or use the present invention.

Applicants clarify that their invention is not directed to administering any selective androgen receptor modulator that interacts with any androgen receptor complex, but rather to administering a selective androgen receptor modulator that exhibits antagonist activity in a hormone-dependent tumor while exhibiting no activity or agonist activity against other non-tumor tissues containing the androgen receptor. This clarification is acknowledged.

Applicants state, on page 16 of their Response, that the test of enablement is whether one skilled in the art could make and use the invention from the disclosure coupled with information known in the art without undue experimentation. This statement is acknowledged. Applicants further state that based on knowledge of compounds having similar physiological or biological activity, one skilled in the art can discern an appropriate method of use without undue experimentation to satisfy 35 U.S.C. 112, first paragraph. This is found unpersuasive due to the unpredictability in the art regarding drug treatments. As stated in MPEP § 2164.03,

> The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling.

The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability.

Applicants state that they have demonstrated through multiple in vitro and in vivo experiments the ability of exemplary SARMs to bind to the androgen receptor and inhibit or antagonize its function in hormone-dependent tumors while exhibiting agonist activity against other, non-tumor tissues containing androgen receptors. This is acknowledged for prostate tumors and various cell lines as seen in Examples 2-13 (pages 86-98). Applicants further state that such pharmacological activity is clearly supportive of the use of these SARMs in additional androgen-receptor mediated disorders as set forth in claim 9, particularly since the modulation of androgen receptor function is an established therapeutic strategy for treatment of such conditions. This is found unpersuasive due to the difficulty and unpredictability of finding effective drugs, as stated by Garrard et al. (col. 1, lines 57-67). It is noted that Applicants did not argue as to why the Garrard et al. reference should not yet support the rejection. In addition, MPEP § 2164.03 states with the following:

The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971). However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Applicants' arguments are also unpersuasive about the claim 9 conditions being an established strategy for the treatment of all of the conditions of claim 9 because this is an allegation without factual support.

Thus, the lack of scope of enablement is maintained for instant claim 9.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. (e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 1-7 and 9 is maintained under 35 U.S.C. 103(a) as being unpatentable over Thorpe et al. (P/N 6,004,554), in view of Zhi et al. (P/N 6,358,947) and Li et al. (P/N 6,469,024).

This rejection is maintained and reiterated for reasons of record.

Thorpe et al. describe treating tumors by using immunological reagents to target tumor-associated vascular endothelial cells in combination with direct targeting of tumor cells (col. 3, lines 45-52 and Table II on col. 25-26). Thorpe et al. describe therapeutic agents that have cytotoxic or anticellular effect by suppressing growth or division of cells (col. 3, lines 57-64). Thorpe et al. describe these methods and compositions as applicable to solid tumors, including carcinomas of the prostate (col. 4, lines 1-11 and Fig. 15A). Thorpe et al. describe a therapeutic method employing an antibody having high selectivity for tumor cells and little or no reactivity with the cell surface of normal endothelial cells (col. 5, lines 30-36). Thorpe et al. describe therapeutics showing no significant reactivity with normal tissues, including kidney, brain, liver, bone marrow, prostate, thyroid, muscle, skin, or other normal organ or tissue (col. 25-26, lines 64-67). Thorpe et al. describe and therefore suggest attaching other agents to target the toxin moiety to a tumor, such as hormones (col. 30, lines 34-43). Thorpe et al. do not specifically mention selective androgen receptor modulators.

Zhi et al. describe compounds that modulate a process mediated by androgen receptors (col. 19, lines 20-23), including male hormone response diseases (col. 19, lines 26-27). Zhi et al. describe a method of treating prostate adenocarcinomas, carcinomas, benign prostatic hypertrophy of prostate, and other hormone-dependent tumors by administering a pharmaceutically effective amount of a compound (col. 20, lines 9-25).

Li et al. describe methods for treating osteoporosis by administering a therapeutically effect amount of a compound which stimulates an increase in muscle mass (col. 5, lines 13-21 and col. 208, lines 50-52). Li et al. describe a method for increasing growth hormone levels by administering a compound (col. 5, lines 7-12). Li et al. describe using the compounds in

combination with a selective androgen receptor modulator to treat, stimulate, and increase muscle mass, as well as reducing cachexia due to cancer (col. 44, lines 47-61). Li et al. describe using the compounds in combination with anti-tumor agents (col. 49, lines 1-4). Li et al. describe treating Alzheimer's disease (col. 45, line 51), anorexia (col. 45, lines 38-39), and muscular atrophy due to physical inactivity and bed rest (col. 46, lines 24-26) by administering a therapeutically effective amount of a compound (col. 45, lines 3-8; col. 208, lines 32-35; and col. 209, lines 7-9).

Thorpe et al. state that significant advances in chemotherapy have been made for some tumors, while other types of tumors resist chemotherapeutic intervention (col. 1, lines 39-41). Thorpe et al. point out the key to developing successful antitumor agents is to design them to selectively kill tumor cells while exerting little effect against normal tissues (col. 1, lines 65-67 and col. 2, line 1). Thorpe et al. state this has been difficult because of the few qualitative differences between neoplastic and normal tissues (col. 2, lines 1-3). Thorpe et al. state much research has been has focused on identifying tumor-specific "marker antigens" (col. 2, lines 3-6). As Thorpe et al. state, modifications can be made without departing from the spirit and scope of their invention (col. 31, lines 48-53), a skilled artisan in the art would have reasonable expectation of success to enhance the methods for inhibiting and treating prostate tumors, as stated by Thorpe et al., by administering various compounds related to prostate, as stated by Zhi et al. and Li et al. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to include the administration of selective androgen receptor modulators (as stated by Zhi et al. and Li et al.) in the methods of inhibiting and treating prostate tumor cells (as stated by Thorpe et al.) with a reasonable expectation of success. The motivation

to do so is given by Thorpe et al. who teach developing successful antitumor agents via selective target agents (col. 1, lines 65-67), and the teaching of Zhi et al. and Li et al. relating to compounds that target androgen receptors.

Thus, Thorpe et al., in view of Zhi et al. and Li et al. motivate the instant invention.

Applicants argue that Zhi et al. and Li et al. do not teach selective androgen receptor modulators (SARMs). This is found unpersuasive as Zhi et al. describe compounds that modulate a process mediated by androgen receptors (col. 19, lines 20-23) which is reasonably interpreted in the broadest sense as selective androgen receptor modulators. Li et al. describe using compounds in combination with selective androgen receptor modulators for various treatments (col. 44, lines 47-61) which is clearly a teaching of selective androgen receptor modulators. Applicants argue that the specification and instant claims require a SARM for use to exhibit antagonist activity in hormone-dependent tumors while exhibiting no activity or agonist activity against other, non-tumor tissues containing the androgen receptor. The instant claims state the methods comprise administering a SARM, as does the prior art references by Li et al. and Zhi et al. (as described above). Applicants submit that the Zhi et al. reference mentions compounds that modulate a process mediated by an androgen receptor, but this activity is secondary to its progesterone receptor modulating activity. This is found unpersuasive as this secondary activity assertion is irrelevant to the instant claims which make no reference to primary or secondary activity. The idea of using SARMs is described in both references by the Li et al. and Zhi et al. Applicants state that the analogs taught by Li et al. are not SARMs defined in Applicants' specification or instant claims. This is found unpersuasive as the instant

claim 9 is broadly and reasonably interpreted include a treatment comprising administering a SARM. The effects of the treatments are described which include reducing cachexia due to cancer (antagonist activity) as well as agonist activity (increase in muscle mass) for a condition such as osteoporosis (see 103 rejection above). Therefore, the limitations in instant claim 9 are clearly met in the 35 U.S.C. 103(a) rejection. As the references state all of the limitations in the instant claims and a reasonable expectation of success to combine the references was described (see 103(a) rejection above), the requirements for a *prima facie* case of obviousness have been met. Therefore, the 35 U.S.C. 103(a) rejection is maintained.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The CM1 Fax Center number is (703) 872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (703) 308-6043. The examiner can normally be reached Monday through Thursday from 8 A.M. to 6:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner Tina Plunkett whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

December 29, 2003

ARDIN H. MARSCHEL
PRIMARY EXAMINER